CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074694

Trade Name : CLOMIPRAMINE HYDROCHLORIDE

Generic Name: Clomipramine Hydrochloride

Sponsor : Taro Pharmaceuticals

Approval Date: December 13, 1996

ANDA 74-694

DEC 31 1996

Taro Pharmaceutical Industries Ltd.
Attention: Timothy A. Anderson (U.S. Agent)
5 Skyline Drive
Hawthorne, NY 10532

Dear Sir:

This is in reference to your abbreviated new drug application dated June 7, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clomipramine Hydrochloride Capsules, 25, 50, and 75 mg.

Reference is also made to your amendments dated March 11, June 3, September 11, September 13, and December 30, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Clomipramine Hydrochloride Capsules 25 mg, 50 mg, and 75 mg are bioequivalent and, therefore therapeutically equivalent, to the listed drug (Anafranil® Capsules 25 mg, 50 mg, and 75 mg, respectively, of Basel Pharmaceuticals. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 12/31/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-694
ANDA #74-694/Division File
Field Copy
HFD-600/Reading File
HFD-93
HFD-610/J.Phillips
HFD-8/P.Savino

Endorsements:

HFD-627/N.Nashed/12-23-96 12/24/96
HFD-613/L.Golson/ 12/24/96
HFD-613/J.Grace/ 12/24/96
HFD-627/P.Schwartz, Ph.D./12-23-96 12/24/96
HFD-617/J.Buccine, PM/12-23-96 12-24-96
X:\NEW\FIRMSNZ\TARO\LTRS&REV\74694.AP2
F/T by MM December 24, 1996
Approval Letter

12/31/96

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-694

3. NAME AND ADDRESS OF APPLICANT

Taro Pharmaceutical Industries Ltd.
14 Hakitor Street
Haifa, 26120, Israel

4. LEGAL BASIS FOR SUBMISSION

See Chemist's Review #1.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clomipramine HCl

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 6/7/95
Amendment 7/19/95
Amendment 3/11/96
Amendment 3/15/96
Amendment 9/11/96
Amendment 9/13/96

10. PHARMACOLOGICAL CATEGORY

Treatment of obsessive-compulsive disorder

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Capsules

14. POTENCY

25, 50, 75 mg

15. CHEMICAL NAME AND STRUCTURE

3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz [b,f]azepine monohydrochloride

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 12/24/96

Supervisor: Paul Schwartz, Ph.D. 12-24-96

TARO

Clomipramine Hydrochloride

Capsules

25 mg

Caution: Federal law prohibits dispensing without prescription.

100 Capsules

Dispense in tight container

DEC 3 1 1996

NDC 51672-4011-1

Do not store above 30°C (86°F). Protect from moisture.

Usual Dosage: See package insert.

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110

Expiration Date

Lot Number

TARO

Clomipramine Hydrochloride

Capsules

50 mg

Caution: Federal law prohibits dispensing without prescription.

100 Capsules

Dispense in tight container

NDC 51672-4012-1

Do not store above 30°C (86°F). Protect from moisture.

Usual Dosage: See package insert.

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110

Expiration Date

Lot Number

TARO

Clomipramine Hydrochloride

Capsules

75 mg

Caution: Federal law prohibits dispensing without prescription.

100 Capsules

Dispense in tight container

NDC 51672-4013-1

Do not store above 30°C (86°F). Protect from moisture.

Usual Dosage: See package insert.

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110

Expiration Date

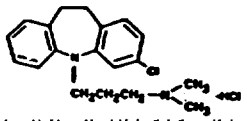
Lot Number

Clomipramine Hydrochloride
Capsules

DESCRIPTION

Clomipramine is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Each capsule for oral administration contains 25 mg, 50 mg, or 75 mg of clomipramine hydrochloride.

Clomipramine is 3-chloro-5-[3-(dimethylamino)propyl]-10, 11-dihydro-5H-dibenz[b,f] azepine monohydrochloride, and its structural formula is:



Clomipramine is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Each capsule contains the following inactive ingredients: Black Iron Oxide (25 mg capsules only), D&C Yellow 10 (25 mg capsules only), FD&C Blue 2 (25 mg capsules only), FD&C Red 3 (25 mg capsules only), Gelatin, Magnesium Stearate, Colloidal Silicon Dioxide, Pregelatinized Starch, Titanium Dioxide, Yellow Iron Oxide (50 mg capsules only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Pharmacokinetics

Absorption/Bioavailability: Clomipramine from clomipramine capsules is as bioavailable as clomipramine from a solution. The bioavailability of clomipramine from capsules is not significantly affected by food.

In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of clomipramine and clomipramine's major active metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and clomipramine/desmethylclomipramine concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of clomipramine occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). After multiple daily doses of 150 mg of clomipramine hydrochloride, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 216 ng/mL) for clomipramine and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for desmethylclomipramine. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: Clomipramine distributes into cerebrospinal fluid (CSF) and brain and into breast milk. Desmethylclomipramine also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of clomipramine is approximately 97%, principally to albumin, and is independent of clomipramine concentration. The interaction between clomipramine and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of clomipramine in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of clomipramine and desmethylclomipramine were only about 0.8-1.3% of the dose administered. Clomipramine does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{ss} and AUC for clomipramine and desmethylclomipramine may increase disproportionately with increasing oral doses suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of clomipramine and desmethylclomipramine are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, clomipramine and desmethylclomipramine may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for clomipramine. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, net accumulation factor for clomipramine is approximately 2.5 and for desmethylclomipramine is 4.8. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of clomipramine hydrochloride have not been determined.

Interactions: Coadministration of haloperidol with clomipramine increases plasma concentrations of clomipramine. Coadministration of clomipramine with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated clomipramine better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of clomipramine were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Clomipramine hydrochloride capsules are indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1988) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of clomipramine for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26-28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking clomipramine experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. Clomipramine treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of clomipramine for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Clomipramine is contraindicated in patients with a history of hypersensitivity to clomipramine or other tricyclic antidepressants.

Clomipramine should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Clomipramine is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of clomipramine hydrochloride use.

The observed cumulative incidence of seizures among patients exposed to clomipramine hydrochloride at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7%, (25 of 3519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of clomipramine greater than 250 mg is limited, given that the plasma concentration of clomipramine may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Caution should be used in administering clomipramine to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, clomipramine had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between clomipramine treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking clomipramine while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking clomipramine in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with clomipramine in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 0.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with clomipramine have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with clomipramine. As with tricyclic antidepressants to which it is closely related, clomipramine may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of clomipramine in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to clomipramine.

Hepatic Changes: During premarketing testing, clomipramine was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with clomipramine, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with clomipramine use. As is the case with tricyclic antidepressants to which clomipramine is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine was used in combination with other drugs. When clomipramine and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with clomipramine in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving clomipramine, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving clomipramine had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of clomipramine with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with clomipramine hydrochloride should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use In Concomitant Illness: As with closely related tricyclic antidepressants, clomipramine should be used with caution in the following:

(1) Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;
(2) Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;
(3) Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;
(4) Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe clomipramine hydrochloride:

(1) The risk of seizure (see WARNINGS);
(2) The relatively high incidence of sexual dysfunction among males (see Sexual Dysfunction);
(3) Since clomipramine may impair the mental and/or physical abilities required for the performance of complex tasks, and since clomipramine is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS);
(4) Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since clomipramine may exaggerate their response to these drugs;
(5) Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;
(6) Patients should notify their physician if they are breast-feeding.

Drug Interactions

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may

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The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS-active drugs (see Information for Patients). Clomipramine should not be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when clomipramine is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin), and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Interactions).

Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clomipramine by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy: *Teratogenic Effects, Pregnancy Category C*

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine until delivery. Clomipramine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clomipramine has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received clomipramine for up to 8 weeks. In addition, 150 adolescent patients have received clomipramine in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with clomipramine may have on the growth and development of children.

The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine in children under the age of 10.

Use in Elderly

Clomipramine has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received clomipramine for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous sys-

tem complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received clomipramine in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued [9% of the total] had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received clomipramine in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving clomipramine (N=322) or placebo (N=319) or children treated with clomipramine (N=46) or placebo (N=44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Clomipramine Hydrochloride
Incidence of Treatment-Emergent Adverse Experience
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(Percentage of Patients Reporting Event)

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Clomipramine (N=322)	Placebo (N=319)	Clomipramine (N=46)	Placebo (N=44)
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7
Libido change	21	3	-	-
Nervousness	18	2	4	2
Myoclonus	13	-	2	-
Increased appetite	11	2	-	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	-
Twitching	7	1	4	5
Impaired concentration	6	2	-	-
Depression	5	1	-	-
Hypertonia	4	1	2	-
Sleep disorder	4	-	9	5
Psychosomatic disorder	3	-	-	-
Yawning	3	-	-	-
Confusion	3	-	2	-
Speech disorder	3	-	-	-
Abnormal dreaming	3	-	-	2
Agitation	3	-	-	-
Migraine	3	-	-	-
Depersonalization	2	-	2	-
Irritability	2	2	2	-
Emotional lability	2	-	-	2
Panic reaction	1	-	2	-
Aggressive reaction	-	-	2	-
Paresis	-	-	2	-
Skin and Appendages				
Increased sweating	20	3	9	-
Rash	8	1	4	2
Pruritus	6	-	2	2
Dermatitis	2	-	-	2
Acne	2	2	-	5
Dry skin	2	-	-	5
Urticaria	1	-	-	-
Abnormal skin odor	-	-	2	-
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	-	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	-
Flatulence	6	3	-	2
Tooth disorder	5	-	-	-
Gastrointestinal disorder	2	-	-	2
Dysphagia	2	-	-	-
Esophagitis	1	-	-	-
Eructation	-	-	2	2
Ulcerative stomatitis	-	-	2	-
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	1	1	2	-
Flushing	8	-	7	-
Hot flushes	5	-	2	-
Chest pain	4	4	7	-
Fever	4	-	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	-	-
Chills	2	1	-	-
Weight decrease	-	-	7	-
Otitis media	-	-	4	5
Asthenia	-	-	2	-
Halitosis	-	-	2	-
Cardiovascular System				
Postural hypotension	6	-	4	-
Palpitation	4	2	4	-
Tachycardia	4	-	2	-
Syncope	-	-	2	-
Respiratory System				
Pharyngitis	14	9	-	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	-	7	2
Epistaxis	2	-	-	2
Dyspnea	-	-	2	-
Laryngitis	-	1	2	-
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	-	-
Micturition frequency	5	3	-	-
Urinary retention	2	-	7	-
Dysuria	2	2	-	-
Cystitis	2	-	-	-
Female Patients Only	(N=162)	(N=167)	(N=19)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	-	-	-
Menstrual disorder	4	2	-	-
Vaginitis	2	-	-	-
Leukorrhea	2	-	-	-
Breast enlargement	2	-	-	-
Breast pain	1	-	-	-
Amenorrhea	1	-	-	-
Male Patients Only	(N=160)	(N=152)	(N=26)	(N=23)
Ejaculation failure	42	2	0	-
Impotence	20	3	-	-
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	-	4	-
Tinnitus	6	-	4	-
Abnormal lacrimation	3	2	-	-
Mydriasis	2	-	-	-
Conjunctivitis	1	-	-	-
Anisocoria	-	-	2	-
Blepharospasm	-	-	2	-
Ocular allergy	-	-	2	-
Vestibular disorder	-	-	2	2
Musculoskeletal				
Myalgia	13	9	-	-
Back pain	6	6	-	-
Arthralgia	3	5	-	-
Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				
Thirst	2	2	-	2

*Events reported by at least 1% of clomipramine patients are included.

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Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				
Thirst	2	2	-	2

*Events reported by at least 1% of clomipramine patients are included.

Other Events Observed During the Premarketing Evaluation of Clomipramine

During clinical testing in the U.S., multiple doses of clomipramine were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to clomipramine who experienced an event of the type cited on at least one occasion while receiving clomipramine. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with clomipramine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* - general edema, increased susceptibility to infection, malaise. *Rare* - dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* - abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* - aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* - abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflex, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* - cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent* - hypothyroidism. *Rare* - goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* - lymphadenopathy. *Rare* - leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* - dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* - fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* - arthrosis. *Rare* - dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent* - abnormal thinking, vertigo. *Infrequent* - abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hypertonesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* - anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, inurism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* - bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* - cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* - alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* - chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* - abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* - blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* - endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* - albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Clomipramine has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with clomipramine discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential clomipramine abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received clomipramine hydrochloride for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for clomipramine in foreign marketing, it is not possible to predict the extent to which clomipramine might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with clomipramine either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, clomipramine's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of clomipramine may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation may be necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated charcoal slurry may help reduce absorption

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OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with clomipramine either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, clomipramine's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of clomipramine may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation may be necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

In the alert patient, the stomach should be emptied promptly by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated charcoal slurry may help reduce absorption of clomipramine.

External stimulation should be minimized to reduce the tendency for convulsions. If anticonvulsants are necessary, diazepam and phenytoin may be useful. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, and, if necessary, a vasopressor agent by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of clomipramine in tissues.

The slow intravenous administration of physostigmine salicylate has been used as a last resort to reverse severe CNS anticholinergic manifestations of overdosage with tricyclic antidepressants; however, it should not be used routinely, since it may induce seizures and cholinergic crises.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of clomipramine in 520 adults, and 91 children and adolescents with OCD. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both clomipramine and its active metabolite, desmethylclomipramine, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with clomipramine hydrochloride should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue clomipramine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of clomipramine after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg - Dark blue cap/light blue body capsules, size 2, with black printing	*Capsules 50 mg - Yellow opaque capsules, size 1, with black printing*	*Capsules 75 mg - White opaque capsules, size 1, with black printing*
Bottles of 100 ..... NDC 51672-4011-1	Bottles of 100 ..... NDC 51672-4012-1	Bottles of 100 ..... NDC 51672-4013-1

Do not store above 30° C (86°F). Protect from moisture.
Dispense in light container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with clomipramine. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

Manufactured by: Taro Pharmaceutical Industries Ltd. Haifa Bay Israel 26110

Revision: September 11, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 74-694

Food and Drug Administration
Rockville MD 20857

JUN 21 1996

Taro Pharmaceuticals U.S.A.
Attention: Michael Kohlbrenner
Six Skyline Drive
Hawthorne, NY 10532

Dear Mr. Kohlbrenner:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act forClomipramine HCl Capsules, 25mg, 50mg and 75mg..

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing should be incorporated into the manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIJ

JUN 18 1996

Clomipramine HCl Capsules
ANDA # 74-694: 25, 50 & 75 mg
Reviewer: Hoainhon Nguyen
WP # 74694a.396

Taro Pharmaceuticals USA
Hawthorne, NY
Submission Date:
March 11, 1996
June 3, 1996

Review of Study Amendments

The firm has submitted amendments to the biostudy results in response to the Division of Bioequivalence's following Deficiency comments:

1. Long term stability study of frozen plasma samples should be submitted to validate fully the biostudy data. Potency of the test and reference biolots should be specified.

2. The dissolution procedure used is not correct. The dissolution testing should be conducted in 500 ml of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 50 rpm. Analytical procedure is Not less than of the labeled amount of clomipramine HCl should be dissolved in 30 minutes.

Dissolution summary tables as given are inadequate. RSD% for 12 units at each sampling time should be given. Range of % dissolution at each sampling time should also be included.

3. Individual plasma concentration and pharmacokinetic parameter data should also be submitted on a diskette.

Firm's Response No. 1: Long term stability data for clomipramine and N-desmethylclomipramine in human plasma and stability data for extracted clomipramine and N-desmethylclomipramine were provided. The data showed that

The stability data are acceptable.

The potency of the test and reference product biostudy lots is given as follows:

Taro's Clomipramine HCl Capsules, 75 mg, Lot No. 094-230, potency of 74.05 mg/capsule or 98.7%.

Basel's Anafranil Capsules, 75 mg, Lot No. 1T163226, potency of 75.20 mg/capsule or 100.3%.

Firm's Response No. 2: The dissolution data obtained under testing conditions specified by the Division of Bioequivalence/USP are given below.

Drug (Generic Name):Clomipramine HCl Capsule Firm: Taro Pharmaceuticals
Dose Strength: 25, 50 & 75 mg
ANDA # 74-694 Submission Date: March 11, 1996

Table - In-Vitro Dissolution Testing

Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 50 No. Units Tested: 12
Medium: HCl 0.1 N Volume: 500 ml
Reference Drug: (Manuf.) Anafranil Capsule, 25, 50 & 75 mg; Basel
Assay Methodology: _____

Results of In-Vitro Dissolution Testing:

	Test Product			Reference Product		
	Lot # 104-297			Lot # 2T156499		
	Strength (mg) 25			Strength (mg) 25		
Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
15	95.4		(3.4)	94.7		(2.2)
30	97.9		(3.3)	96.5		(2.2)
45	99.0		(1.6)	97.0		(2.2)
60	99.6		(1.7)	97.3		(2.3)

Test Product		Reference Product	
Lot # 104-298		Lot # 1T157515	
Strength (mg) 50		Strength (mg) 50	

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
15	94.5		(3.1)	95.3		(3.7)
30	98.0		(2.1)	98.1		(2.8)
45	98.2		(3.0)	99.0		(2.7)
60	98.5		(2.5)	99.7		(2.4)

Test Product	Reference Product
Lot # 094-230	Lot # 1T163226
Strength (mg) 75	Strength (mg) 75

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
15	93.4		(5.5)	92.8		(6.5)
30	96.8		(4.3)	98.4		(2.8)
45	97.9		(3.4)	98.8		(2.9)
60	98.3		(3.0)	99.2		(2.6)

Specifications:
NLT @ 30 min

The dissolution data are acceptable.

Firm's Response No. 3: The firm has submitted a diskette of clomipramine individual subject plasma concentration data and pharmacokinetic parameters (Fasting Study). The N-desmethylclomipramine data, were not included in this diskette. Upon a request by telephone (May 31, 1996), the metabolite data were submitted in another diskette (June 3, 1996) (Fasting Study).

Individual plasma concentration data of both clomipramine and N-desmethylclomipramine were spot-checked. ANOVA was run for lnAUCs and lnCMAX for both clomipramine and its metabolite and 90% confidence intervals for these parameters were calculated based on the ANOVA results.

90% confidence intervals were verified. However, the following values, as given in the firm's study report, were found incorrect and corrected (in bold) in the summary tables below (Tables I and III of the original review dated February 15, 1996): Geometric LS means of AUC(0-Inf) of clomipramine of both test and reference products, and geometric LS means of AUC(0-T) and AUC(0-Inf) of N-desmethylclomipramine of both test and reference products and geometric LS mean of CMAX of N-desmethylclomipramine of the test product.

Table I

Clomipramine Comparative Pharmacokinetic Parameters
Dose = 75 mg; n = 30

Parameters	Taro Mean (CV)	Anafranil[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	978.6*	1034*	[0.80;1.12]	0.95
AUC (0-Inf) ng.hr/ml	**1140***	**1102***	[0.98;1.09]	**1.03**
CMAX(ng/ml)	51.70*	54.79*	[0.82;1.09]	0.94
TMAX (hrs)	4.63(26)	4.77(24)		
KEL (1/hrs)	0.03(39)	0.03(48)		
T1/2 (hrs)	30.26(38)	31.90(44)		

*Least Squares geometric means

Table III

N-Desmethylclomipramine Comparative Pharmacokinetic Parameters
Dose = 75 mg; n = 30

Parameters	Taro Mean (CV)	Anafranil[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	720.3*	690.9*	[0.98;1.11]	1.04
AUC (0-Inf) ng.hr/ml	889.7*	870.2*	[0.96;1.09]	1.02
CMAX(ng/ml)	11.48*	10.95*	[1.01;1.09]	1.05
TMAX (hrs)	13.38(81)	15.87(104)		
KEL (1/hrs)	0.02(64)	0.02(60)		
T1/2 (hrs)	62.53(77)	64.15(80)		

*Least Squares geometric means

Recommendations: (The recommendations are based on the review of submissions dated June 7, 1995, March 11, 1996 and June 3, 1996)

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Taro Pharmaceutical on the test product, Clomipramine HCl Capsules, 75 mg, lot # 094-230, comparing it with the reference product, Anafranil[R] Capsules, 75 mg, lot # 1T163226, have been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Taro Pharmaceutical on its Clomipramine HCl Capsules, 75 mg, 50 mg and 25 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of 0.1N HCl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. The firm has demonstrated that the formulation of its Clomipramine HCl Capsules, 25 mg and 50 mg, is proportionally similar to the 75 mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 25 mg and 50 mg capsules is granted. The firm's Clomipramine HCl Capsules, 25 mg and 50 mg, are therefore deemed bioequivalent to Anafranil® Capsules, 25 mg and 50 mg, respectively, manufactured by Basel Pharmaceuticals.

6/10/96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 6/11/96

Concur: for Keith Chan Date: 6/18/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

LAB NP# 74694 a. 396 Attachment 1 of 6

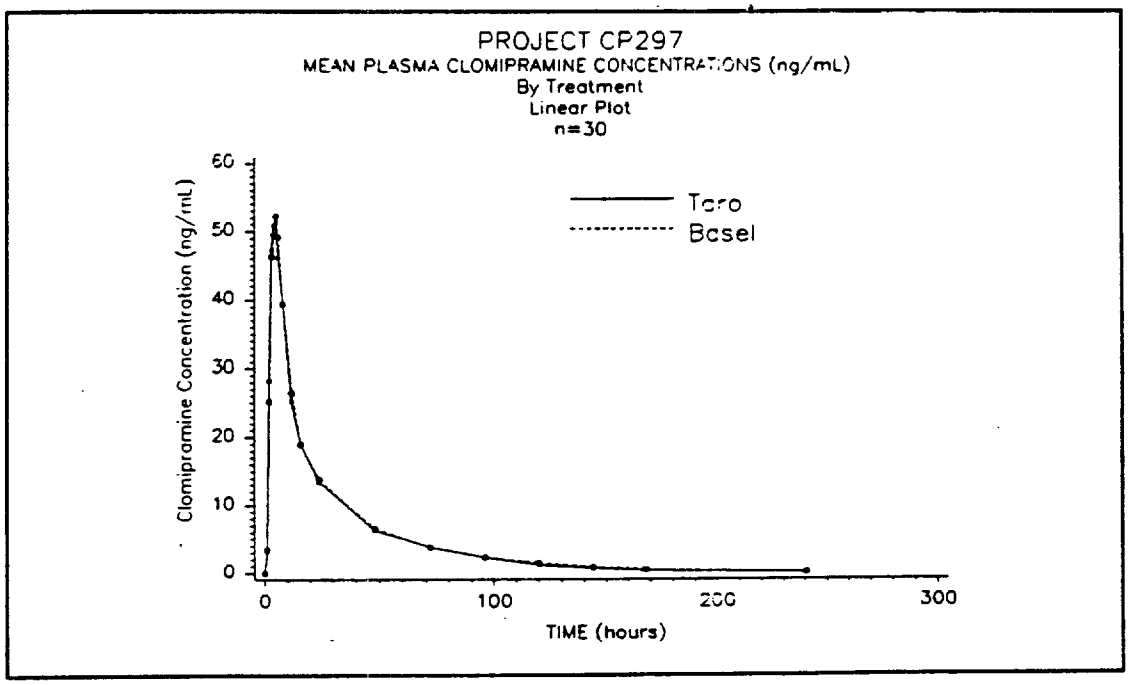


Figure 1

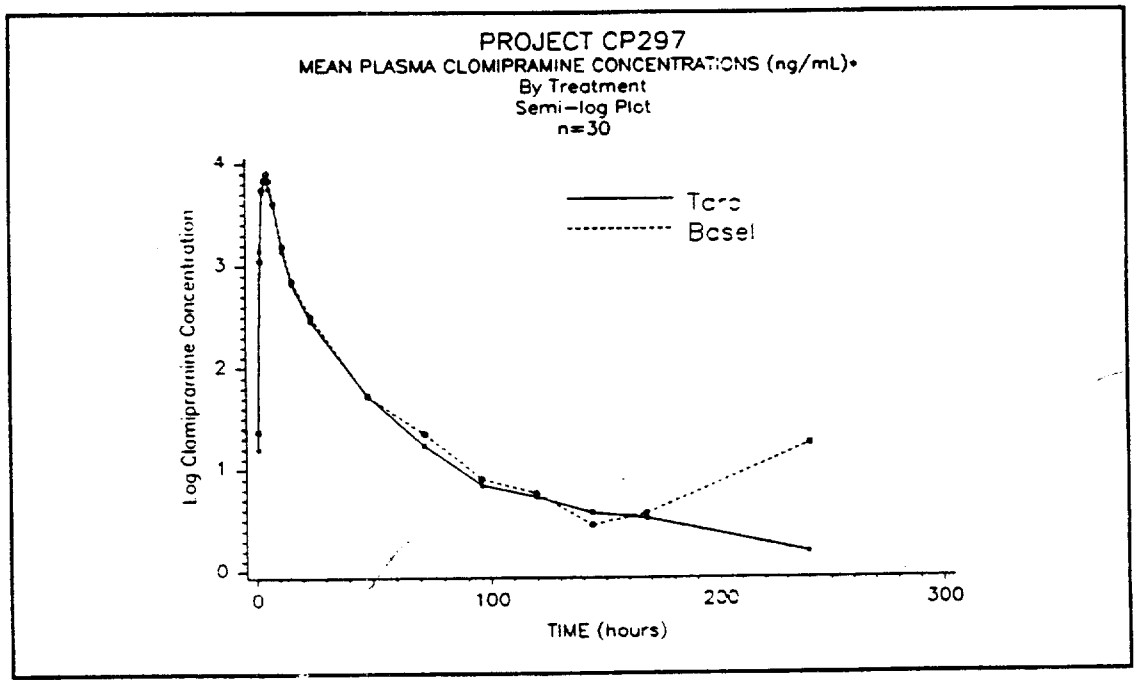


Figure 2

* Note that the apparent difference in plasma concentrations at 240 hour is due to BLQ levels in some subjects.

LAB

WP # 74694 q. 396 Attachment 2 of 6

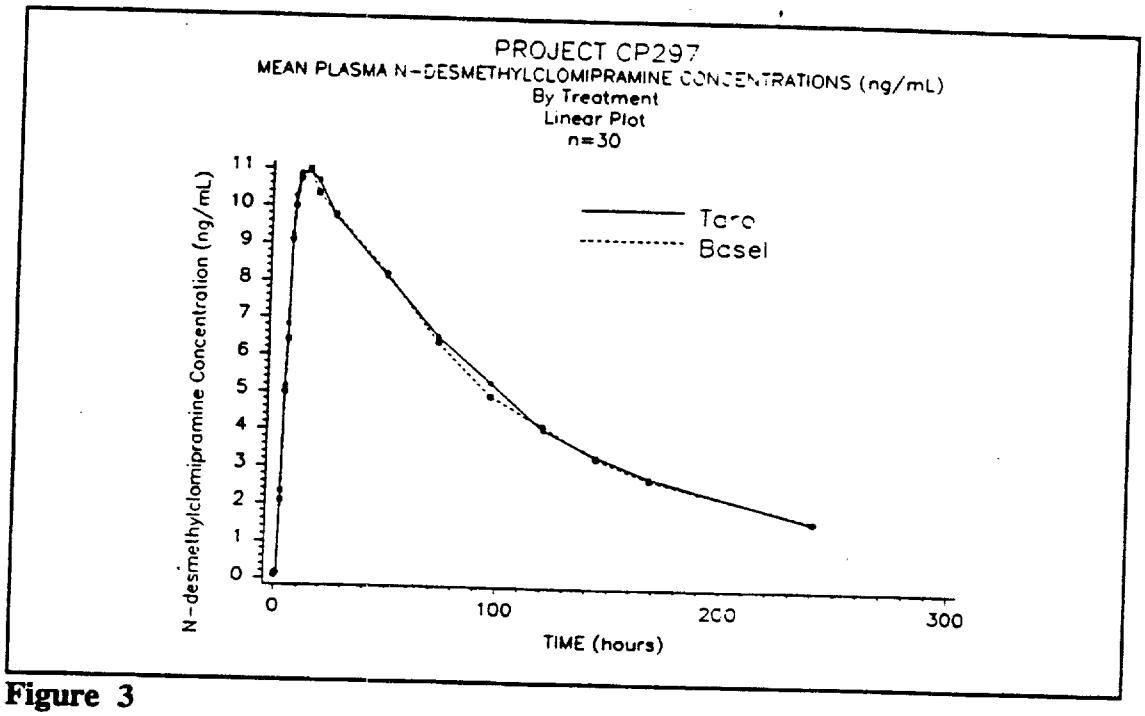


Figure 3

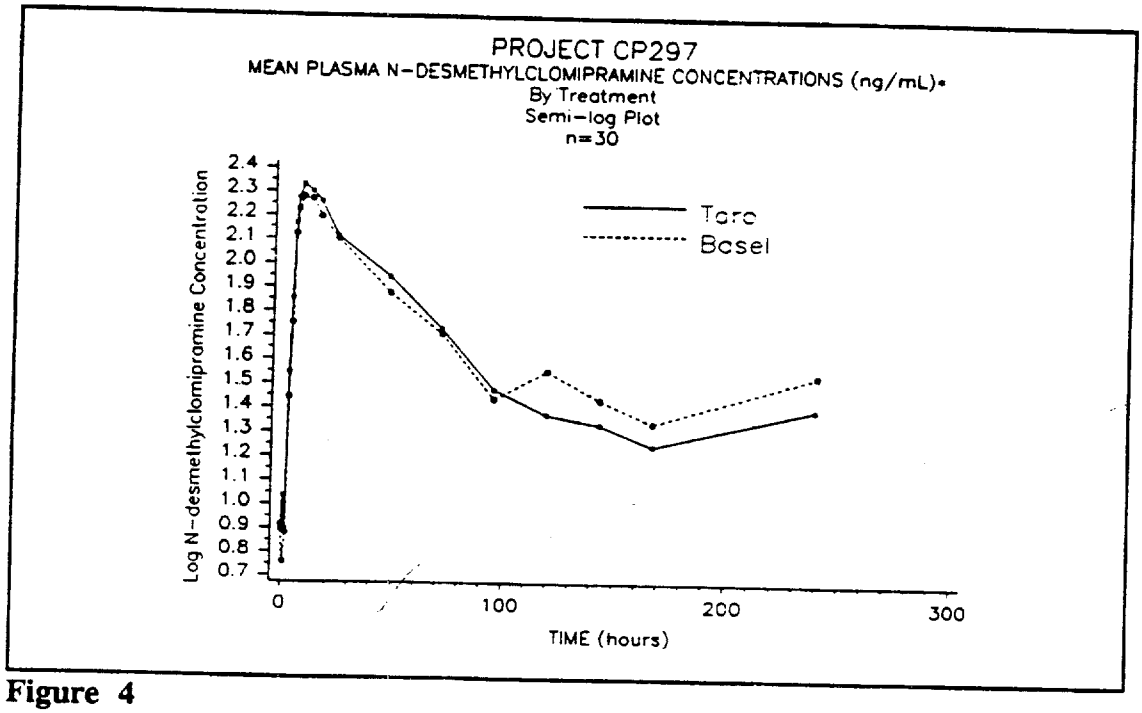


Figure 4

* Note that the apparent difference in the plasma concentrations after 96 hours is due to BLQ levels in some subjects.

B

WP# 74694 q. 396 Attachment 3 of 6

FIGURE 1

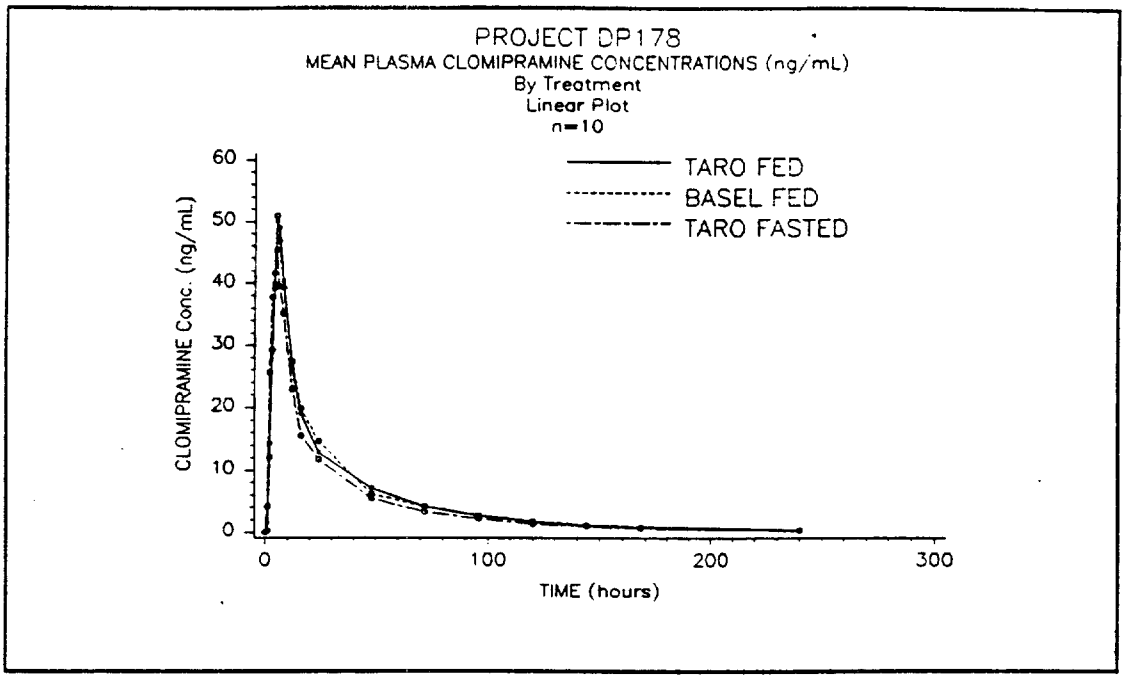
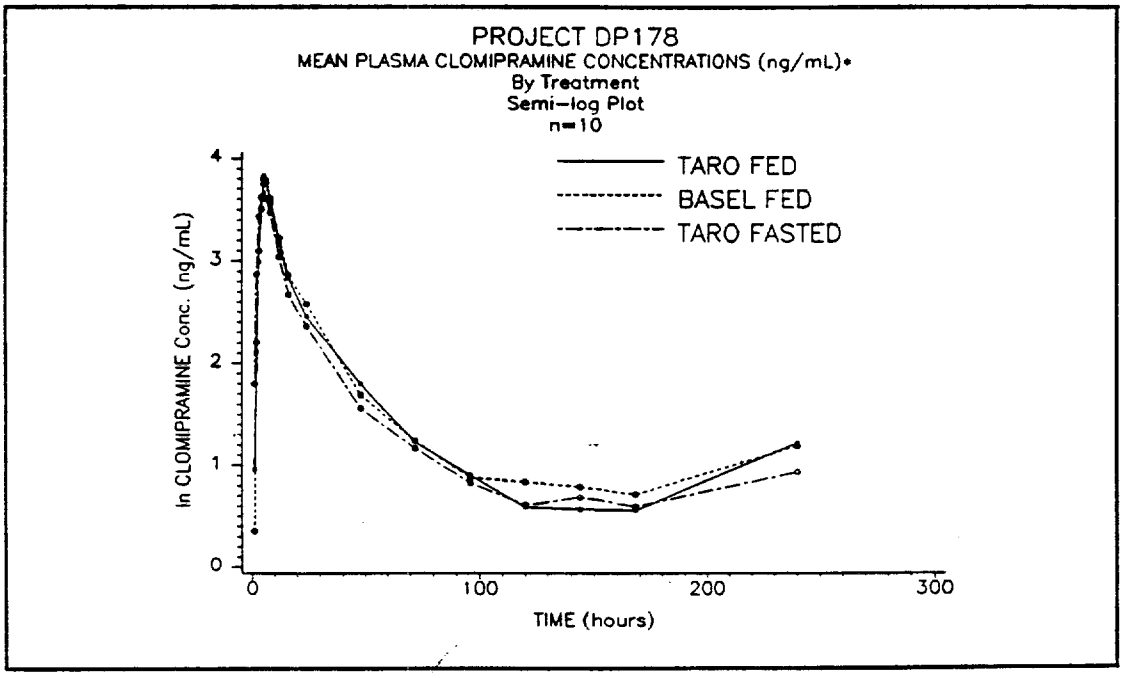


FIGURE 2



* Note that the apparent difference in plasma concentrations after 96 hours is due to BLQ levels in some subjects.

B

WP # 4694a. 396 Attachment 4 of 6

FIGURE 3

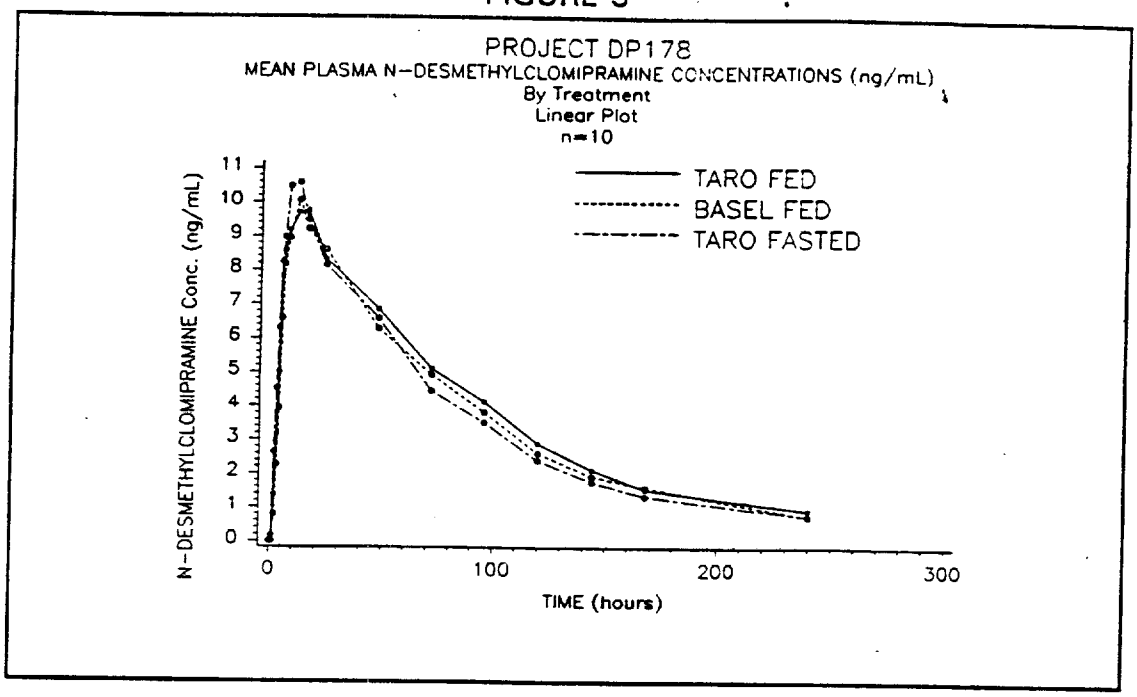
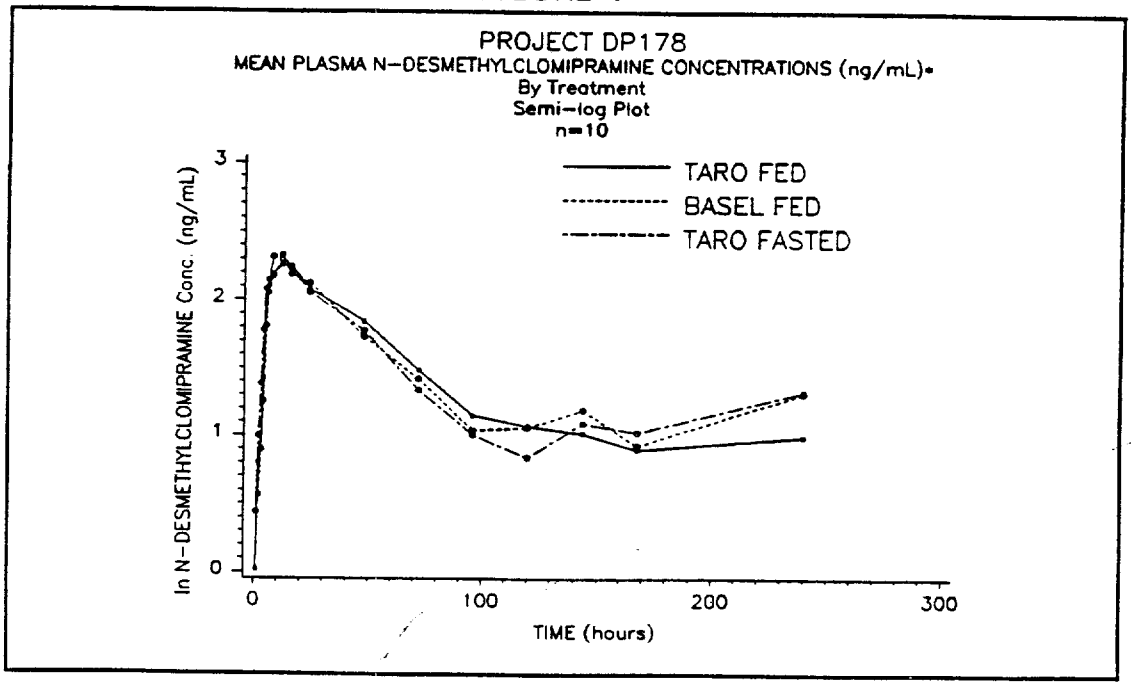


FIGURE 4



* Note that the apparent difference in plasma concentrations after 96 hours is due to BLQ levels in some subjects.

wf # ~~74694 sdw. 695~~ Attachment (5 of 6)
74694 a. 396

The following is a full statement of the composition of the dosage formulation for Clomipramine Hydrochloride Capsules, 25 mg test batch included in this application:

Item	mg/Capsule	Quantity/Batch
Clomipramine Hydrochloride BP	25 mg	
Pregelatinized Starch NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Capsule Shell	—	

The following is a full statement of the composition of the dosage formulation for Clomipramine Hydrochloride Capsules, 50 mg test batch included in this application:

Item	mg/Capsule	Quantity/Batch
Clomipramine Hydrochloride BP	50 mg	
Pregelatinized Starch NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Capsule Shell	—	

Wf# ~~74694 sdw. 659~~ Attachment (6 of 6)
74694 a. 396

The following is a full statement of the composition of the dosage formulation for Clomipramine Hydrochloride Capsules, 75 mg test batch included in this application:

Item	mg/Capsule	Quantity/Batch
Clomipramine Hydrochloride BP	75 mg	
Pregelatinized Starch NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Capsule Shell	—	

Unit and Batch Composition

The per batch quantity listed for each ingredient represents the total amount of that ingredient that is actually measured out for the batch. This quantity may, for some ingredients, differ slightly from the theoretical quantity calculated by multiplying the unit composition by the batch size. The reason for this is that all amounts to be measured out are expressed in increments limited to accuracy of the equipment on which they are weighed. In no way is the difference between actual and theoretical per batch quantities related to or provided for in the incorporation of a range for individual ingredients. Exact ingredient amounts are measured out for every batch, as required by the Master Product and Control Record, attached in Section XI at pages 3354.

FEB 15 1996

D,V

Clomipramine HCl Capsules
ANDA # 74-694: 25, 50 & 75 mg
Reviewer: Hoainhon Nguyen
WP # 74694sdw.695

Taro Pharmaceuticals USA
Hawthorne, New York
Submission Date:
June 7, 1995

Review of Two Bioequivalence Studies, Dissolution Data and Waiver Requests

I. Background:

Clomipramine hydrochloride is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. The drug is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). Clomipramine is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission by possibly inhibiting the reuptake of serotonin (5-HT). Clomipramine hydrochloride is freely soluble in water.

Following an oral dose of clomipramine hydrochloride, maximum plasma concentrations occur within 2-6 hours (mean 4.7 hr). THe drug distributes into cerebrospinal fluid and brain and into breast milk. The protein binding of the drug is approximately 97%, principally to albumin, and independent of clomipramine hydrochloride concentration. The bioavailability of the drug from capsules is not significantly affected by food. In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curve (AUC) of clomipramine and its major metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. This finding suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited.

Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on Obsessive-Compulsive Disorder behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. Following a 150-mg dose, the half-life of clomipramine ranges from 19 to 37 hours (mean 32 hr) and that of desmethylclomipramine ranges from 54 to 77 hours (mean 69 hr).

The most commonly observed adverse effects associated with clomipramine were gastrointestinal complaints including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints including changed libido, ejaculatory failure, impotence, a micturition disorder; and other miscellaneous complaints including fatigue, sweating, increased appetite, weight gain and visual changes.

Clomipramine Hydrochloride is available commercially as Anafranil^{R} oral capsule, 25 mg, 50 mg and 75 mg, manufactured by Basel Pharmaceuticals.

The firm has submitted a fasting and a non-fasting single-dose bioequivalence study comparing its clomipramine HCl capsules, 75 mg, with Basel's Anafranil^{R} 75-mg capsules; comparative dissolution data for the test and reference products of 25, 50 and 75 mg strengths; comparative formulations of the 25, 50 and 75 mg strengths of the test product; and requests of waiver of in-vivo bioequivalence requirements for the 25 and 50 mg strengths of the test product.

II. Bioequivalence Studies:

A. Fasting Bioequivalence Study (Protocol No. CP297)

Two-Way Crossover Bioequivalence Study of Taro and Basel (Anafranil^{R}) 75 mg Clomipramine HCl Capsules in Fasting Volunteers

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Taro's Clomipramine HCl Capsules, 75 mg, and Basel's Anafranil[R] Capsules, 75 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at the between October 27, 1994 and December 10, 1994. The principal investigator was samples were assayed by the under the supervision of between February 7, 1995 and March 10, 1995.

Demographics:

Normal, healthy, non-smoking male volunteers between 19-41 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 163 - 200 lbs and 62.1 - 92.5 in., respectively. Thirty-six subjects were initially entered in the study and completed Period 1. Twelve of these subjects vomited after dosing. The protocol was amended to add 16 more subjects.

Inclusion criteria:

Subjects especially did not have any history of: significant cardiovascular, hepatic, renal, CNS, hematological or gastrointestinal disease; alcoholism or drug abuse within the last year; depression or anti-depressant therapy; psychosis; urinary retention; glaucoma; prostatic hypertrophy; convulsive or seizure disorders; thyroid disease and hypersensitivity or idiosyncratic reaction to clomipramine or any other tricyclic antidepressants belonging to the dibenzazepine group.

Restrictions:

They were free of all medications at least 14 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed for 24 hours prior to and throughout the period of sample collection. The subjects fasted for 10 hours prior to and 4 hours after each drug administration. The washout duration between the two phases was 21 days for Subjects No. 1-36 and 23 days for Subjects No. 37-52. Duration of confinement was 10 hours pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 75 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Taro's clomipramine HCl capsules, 75 mg, lot # 094-230 (Batch size , potency not given).

Reference product: Basel's Anafranil^{R} capsules, 75 mg, lot # 1T163226 (Potency not given).

Blood samples were collected at predose, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 120.0, 144.0, 168.0 and 240.0 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -10^{0}C until shipping to the analytical laboratory.

Assay Methodology:

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. Group effects between subgroups of participants were assessed before the data from both groups were pooled. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Thirty-six subjects were initially entered in the study. Following Period I with twelve of these subjects vomited after dosing, sixteen additional subjects were entered in the study. Of 51 subjects completing the study, a total of 21 subjects vomited during Period I and/or II. The samples of the vomiting subjects were not analyzed. The study results were based on data from a total of 30 nonvomiting subjects.

Clomipramine:

The treatment-by-group interaction term was found non-significant and the data from the first and second group of subjects was pooled together.

There was no significant difference (alpha=0.05) between treatments for AUC (0-Infinity), lnAUC(0-T), lnAUC(0-Infinity), lnCMAX and TMAX. The results are summarized in the tables below:

Table I

Clomipramine Comparative Pharmacokinetic Parameters
Dose = 75 mg; n = 30

Parameters	Taro Mean (CV)	Anafranil[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	978.6*	1034*	[0.80;1.12]	0.95
AUC (0-Inf) ng.hr/ml	1113*	1090*	[0.98;1.09]	1.02
CMAX(ng/ml)	51.70*	54.79*	[0.82;1.09]	0.94
TMAX (hrs)	4.63(26)	4.77(24)		
KEL (1/hrs)	0.03(39)	0.03(48)		
T1/2 (hrs)	30.26(38)	31.90(44)		

*Least Squares geometric means

Table II

Comparative Mean Plasma Levels of Clomipramine (n = 30)

ng/ml(CV)

Dose = 75 mg

Hour	Taro	Anafranil[R]
0	0	0
1.00	3.19(143)	3.45(117)
2.00	28.21(57)	25.21(65)
3.00	47.32(44)	46.35(45)
4.00	50.82(39)	49.44(35)
5.00	51.35(35)	52.21(33)
6.00	46.17(36)	49.19(33)
8.00	39.45(36)	39.38(34)
12.00	25.29(39)	26.44(41)
16.00	19.11(47)	18.96(41)
24.00	13.48(49)	13.85(47)
48.00	6.36(57)	6.59(61)
72.00	3.79(72)	3.83(75)
96.00	2.33(93)	2.32(87)
120.0	1.23(140)	1.49(114)
144.0	0.74(163)	0.90(135)
168.0	0.36(219)	0.46(210)
240.0	0.08(387)	0.12(548)
AUC(0-T)ng.hr/ml	1147(52)	1173(51)
AUC(0-Inf)ng.hr/ml	1238(48)	1238(53)
CMAX	56.08(35)	57.71(33)

N-Desmethylclomipramine:

The treatment-by-group interaction term was found non-significant and the data from the first and second group of subjects was pooled together.

There was no significant difference (alpha=0.05) between treatments for AUC (0-T),AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX and TMAX. The results are summarized in the tables below:

Table III

N-Desmethylclomipramine Comparative Pharmacokinetic Parameters
Dose = 75 mg; n = 30

Parameters	Taro Mean (CV)	Anafranil[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	736.9*	690.9*	[0.98;1.11]	1.07
AUC (0-Inf) ng.hr/ml	918.4*	923.1*	[0.96;1.09]	0.99
CMAX(ng/ml)	11.50*	10.95*	[1.01;1.09]	1.05
TMAX (hrs)	13.38(81)	15.87(104)		
KEL (1/hrs)	0.02(64)	0.02(60)		
T1/2 (hrs)	62.53(77)	64.15(80)		

*Least Squares geometric means

Table IV

Comparative Mean Plasma Levels of N-Desmethylclomipramine (n = 30) ng/ml(CV)

Dose = 75 mg

Hour	Taro	Anafranil[R]
0	0.17(388)	0.08(548)
1.00	0.19(392)	0.14(386)
2.00	2.33(78)	2.09(97)
3.00	5.13(57)	5.00(64)
4.00	6.81(48)	6.40(44)
5.00	9.21(45)	9.09(42)
6.00	10.25(46)	9.99(38)
8.00	10.86(47)	10.73(44)
12.00	10.93(54)	10.98(49)
16.00	10.69(55)	10.35(51)
24.00	9.73(66)	9.79(58)
48.00	8.15(82)	8.22(82)
72.00	6.53(101)	6.37(99)
96.00	5.32(116)	4.95(111)
120.0	4.07(130)	4.16(124)
144.0	3.38(150)	3.31(139)
168.0	2.81(159)	2.76(156)
240.0	1.67(210)	1.69(190)
AUC(0-T)ng.hr/ml	1169(104)	1154(99)
AUC(0-Inf)ng.hr/ml	1673(128)	1622(117)
CMAX	12.25(49)	12.07(44)

Adverse Effects:

All complaints were judged by the investigator to be mild or moderate in severity. The list of the adverse reactions is attached.

B. Non-Fasting Bioequivalence Study (Protocol No. DP178)

Three-Way Crossover Bioavailability Study of Taro and Basel (Anafranil^{R}) 75 mg Clomipramine HCl Capsules in Fed and Fasting Volunteers

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Taro's Clomipramine HCl Capsules, 75 mg, and Basel's Anafranil^{R} Capsules, 75 mg, in a non-fasting single dose, three-treatment, three-period crossover study design.

Study Investigators and Facilities:

The study was conducted at the between October 13, 1994 and November 25, 1994. The principal investigator was samples were assayed by under the supervision of between March 9, 1995 and March 27, 1995.

Demographics:

Eighteen normal, healthy, non-smoking male volunteers between 20-44 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, three-sequence randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 157 - 186 lbs and 62.3 - 100.0 in., respectively.

Inclusion criteria:

Same as in Protocol No. CP297 above.

Restrictions:

Same as in Protocol No. CP297 above except that:

(i) For non-fasting treatments (Treatments A and B), the subjects fasted overnight for 9.5 hours and were given a standard breakfast 30 minutes before dosing. The standard breakfast consisted of 240 ml of whole milk, one fried egg, one buttered English muffin, one slice of Canadian bacon, one slice of American cheese, one serving of hash brown potatoes and 180 ml of orange juice.

(ii) For fasting treatment (Treatment C), the subjects fasted overnight for 10 hours before dosing and for 4 hours after dosing.

Treatments and Sampling:

The three treatments consisted of a single 75 mg dose of either the test product or reference product taken orally with 240 ml of water under non-fasting conditions (Treatments A and B) or fasting conditions (Treatment C).

Test Product: Taro's clomipramine HCl capsules, 75 mg, lot # 094-230 (Batch size potency not given).

Reference product: Basel's Anafranil^{R} capsules, 75 mg, lot # 1T163226 (Potency not given).

Blood samples were collected at predose, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 120.0, 144.0, 168.0 and 240.0 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -10^{0}C until shipping to the analytical laboratory.

III. Assay Methodology:

IV. Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Eighteen subjects were initially entered in the study. A total of 8 subjects vomited during Period I, II and/or III. The samples of the vomiting subjects were not analyzed. The study results were based on data from a total of 10 nonvomiting subjects.

Clomipramine:

There was no significant difference (alpha=0.05) between treatments for CMAX, lnCMAX, TMAX and KEL. There were significant differences between treatments for AUC(0-T) (p=0.0058), AUC(0-Infinity) (p=0.0062), lnAUC(0-T) (p=0.0015) and lnAUC(0-Infinity) (p=0.0033). The results are summarized in the tables below:

Table V

Clomipramine Comparative Pharmacokinetic Parameters
Dose = 75 mg; n = 10

Parameters	Taro (fed) Mean (CV)	Anafranil® (fed) Mean (CV)	Taro (fasted) Mean (CV)	Ratio T/R (fed/fed)
AUC (0-T) ng.hr/ml	1026*	1010*	877.8*	1.02
AUC (0-Inf) ng.hr/ml	1109*	1040*	915.9*	1.07
CMAX(ng/ml)	49.88*	46.86*	44.95*	1.06
TMAX (hrs)	5.7(17)	5.3(24)	4.8(16)	
KEL (1/hrs)	0.020(37)	0.022(35)	0.025(52)	
T1/2 (hrs)	44.42(82)	37.80(65)	36.78(65)	

*Least Squares geometric means

Table VI
Comparative Mean Plasma Levels of Clomipramine (n = 10)
ng/ml(CV)
Dose = 75 mg

Hour	Taro(fed)	Anafranil[R](fed)	Taro(fasted)
0	0	0	0
1.00	1.50(203)	0.29(212)	4.16(165)
2.00	14.29(99)	12.13(123)	25.60(82)
3.00	28.96(89)	29.27(70)	37.73(62)
4.00	39.88(62)	39.19(61)	41.61(48)
5.00	50.09(44)	50.93(51)	45.34(41)
6.00	49.01(45)	46.83(43)	39.56(42)
8.00	40.43(40)	39.26(47)	35.13(46)
12.00	26.41(41)	27.39(40)	22.93(47)
16.00	19.07(45)	19.83(51)	15.53(37)
24.00	12.86(46)	14.62(46)	11.73(48)
48.00	7.13(60)	6.16(49)	5.44(52)
72.00	4.17(69)	4.16(72)	3.27(70)
96.00	2.67(82)	2.65(88)	2.18(101)
120.0	1.70(95)	1.73(140)	1.32(130)
144.0	1.11(160)	1.17(192)	0.94(169)
168.0	0.84(172)	0.79(212)	0.66(202)
240.0	0.38(300)	0.33(316)	0.26(316)
AUC(0-T)ng.hr/ml	1188(56)	1191(60)	1028(61)
AUC(0-Inf)ng.hr/ml	1327(66)	1252(69)	1095(68)
CMAX	53.96(42)	52.07(48)	48.72(43)

N-Desmethylclomipramine:

There was no significant difference (alpha=0.05) between treatments for AUC (0-T),AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX and TMAX. The results are summarized in the tables below:

Table VII

N-Desmethylclomipramine Comparative Pharmacokinetic Parameters
Dose = 75 mg; n = 10

Parameters	Taro (fed) Mean (CV)	Anafranil[R] (fed) Mean (CV)	Taro (fasted) Mean (CV)	Ratio T/R (Fed/fed)
AUC (0-T) ng.hr/ml	751.3*	697.7*	690.1*	1.08
AUC (0-Inf) ng.hr/ml	887.0*	821.3*	823.8*	1.08
CMAX(ng/ml)	10.79*	10.41*	10.88*	1.04
TMAX (hrs)	13.5(94)	14.8(81)	9.8(24)	
KEL (1/hrs)	0.015(43)	0.016(40)	0.015(43)	
T1/2 (hrs)	60.80(70)	54.57(59)	60.32(64)	

*Least Squares geometric means

Table VIII

Comparative Mean Plasma Levels of N-desmethylclomipramine(n=10)
ng/ml(CV)
Dose = 75 mg

Hour	Taro (fed)	Anafranil[R] (fed)	Taro (fasted)
0	0	0	0
1.00	0.10(316)	0	0.16(316)
2.00	1.35(142)	0.79(157)	2.63(99)
3.00	3.14(104)	2.26(81)	4.52(53)
4.00	5.00(66)	3.92(58)	6.31(41)
5.00	7.82(43)	6.58(40)	8.24(28)
6.00	8.58(35)	8.16(33)	8.96(35)
8.00	9.17(22)	8.94(20)	10.47(27)
12.00	9.68(21)	10.05(22)	10.58(28)
16.00	9.74(26)	9.20(27)	9.47(26)
24.00	8.31(31)	8.59(27)	8.14(32)
48.00	6.85(42)	6.29(49)	6.59(54)
72.00	5.11(57)	4.93(64)	4.46(61)
96.00	4.14(78)	3.83(88)	3.52(83)
120.0	2.90(93)	2.62(111)	2.40(102)
144.0	2.12(131)	1.93(133)	1.76(135)
168.0	1.54(146)	1.61(145)	1.35(159)
240.0	0.93(190)	0.75(211)	0.77(215)
AUC(0-T)ng.hr/ml	886.1(64)	836.3(67)	817.6(67)
AUC(0-Inf)ng.hr/ml	1114 (82)	1020 (76)	1030 (80)
CMAX	11.06(23)	10.64(22)	11.25(26)

Adverse Effects:

The complaints are summarized in the attachments. Intensity of the reactions was not noted.

III. Dissolution Testing:

The dissolution procedure used is not correct. The dissolution testing should be conducted in 500 ml of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 50 rpm. Analytical procedure is Not less thar of the labeled amount of clomipramine HCl should be dissolved in 30 minutes.

Dissolution summary tables as given are inadequate. RSD% for 12 units at each sampling time should be given. Range of % dissolution at each sampling time should also be included.

IV. Formulation Comparison:

Formulation of the 25 mg and 50 mg strengths of the test product are proportionally similar to the 75 mg strength of the test product. See attachment.

V. Deficiencies:

1. Long term stability study of frozen plasma samples should be submitted to validate fully the biostudy data. Potency of the test and reference biolots should be specified.

2. The dissolution procedure used is not correct. The dissolution testing should be conducted in 500 ml of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 50 rpm. Analytical procedure is Not less than of the labeled amount of clomipramine HCl should be dissolved in 30 minutes.

Dissolution summary tables as given are inadequate. RSD% for 12 units at each sampling time should be given. Range of % dissolution at each sampling time should also be included.

3. Individual plasma concentration and pharmacokinetic parameter data should also be submitted on a diskette.

VII. Recommendations:

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Taro Pharmaceutical Industries Ltd. on the test product, Clomipramine HCl Capsules, 75 mg, lot # 094-230, comparing it with the reference product, Anafranil[R] Capsules, 75 mg, lot # 1T163226, have been found incomplete by the Division of Bioequivalence due to the reason cited in the Deficiency No. 1 above.

2. The in-vitro dissolution testing conducted by Taro Pharmaceutical on its Clomipramine HCl Capsules, 25 mg, 50 mg and 75 mg, has been found incomplete due to the reason cited in the Deficiency No. 2 above.

The firm should be informed of the Recommendations and Deficiencies.

2/15/96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 2/15/96

Concur: I/f see ltr memo 2-16-96 Date:
Keith Chan, Ph.D.
Director, Division of Bioequivalence
conflict of interest
Rebi Remark with sign approval

cc: ANDA # 74-694 (original, duplicate), HFD-630(OGD), HFD-600(Hare), HFD-652(Huang, Nguyen), HFD-344(CViswanathan), Drug File, Division File

HNguyen/11-27-95/WP #74694sdw.695

Attachments: 6 pages

LAB

WP # 74694sdw.695 Attachment (p 1 of 6)

TABLE C2

	Number of Complaints Recorded by Relationship to Drug			
	Taro Formulation A		Basel Formulation B	
Complaint	Probably/Possibly	Remote	Probably/Possibly	Remote
Acne				1
Burning sensation stomach	1		1	
Blurry vision	1		1	
Chest pain				1
Chills	1		2	
Constipation				1
Difficulty ejaculating		1		
Difficulty having a bowel movement	1			
Difficulty passing urine	1			
Difficulty urinating	1			
Disoriented			2	
Dizziness	11		10	2
Drowsiness	3		2	
Dry mouth			1	
Dry throat	1			
Feels like ears are blocked	1			
Feeling cold				1
Feeling hot	1			
Feeling lazy	1			
Feeling warm	2		1	
General muscle stiffness	1			
General weakness	1			
Headache	9	5	7	3
Lightheaded	5		5	
Loose stools	11	2	8	1
Loss of appetite	3		1	1
Muscle spasm				1
Metallic taste in mouth			1	
Nausea	21	1	19	1
Numbness			1	

Continued next page...

WPA 74 694 sdw. 695 Attachment (2 of 6)

TABLE C2

	Number of Complaints Recorded by Relationship to Drug			
	Taro Formulation A		Basel Formulation B	
Complaint	Probably/Possibly	Remote	Probably/Possibly	Remote
Numbness lower jaw			1	
Pain in abdomen		1		
Perspiring	1			
Pressure left eye	1			
Pressure in sinuses	1			
Red rash inner right arm				1
Runny nose		1		
Sleep disturbances				1
Stiff jaw	1			
Stomach cramps		1		
Stomach muscle ache	1			
Tiredness			2	
Tremors in mouth	1			
Trouble sleeping	2	4	1	
Unable to concentrate	2			
Upset stomach	1			
Vomited	21		26	
Yawning	1			

WP # 74694 sdw. 695 Attachment (3 of 6)

TABLE C2

NUMBER OF COMPLAINTS

Complaint	Number of Complaints Recorded by Relationship to Drug					
	Treatment A		Treatment B		Treatment C	
	Probably/ Possibly	Remote	Probably/ Possibly	Remote	Probably/ Possibly	Remote
Abdominal pain						1
Acceleration of heart beat		1				
Anxious			1			
Back pain				1		
Burning			1			
Burning sensation in stomach					1	
Chattering teeth					1	
Chest pain		1				
Chills					3	
Dizzy	1				2	
Dry mouth			1		2	
Dry throat	1		1			
Drowsy	1	1	2		1	
Feeling nervous inside					1	
Feels hot	1				1	
Feels warm	1					
Headache	3	4		4	2	
Insomnia				1		
Jaw feels tight	1					
Lightheadedness	1		2		2	
Loss of appetite		1	1	1	1	1
Loose stools	2		1		1	
Loss of balance	1					
Nausea	8	1	5	2	9	
Pain in calves				1		

Complaint	Number of Complaints Recorded by Relationship to Drug					
	Treatment A		Treatment B		Treatment C	
	Probably/ Possibly	Remote	Probably/ Possibly	Remote	Probably/ Possibly	Remote
Pain - upper back		1				
Palpitations					1	
Shaky	1				2	
Tiredness		1			1	
Unable to have a bowel movement					1	1
Unusual dreams	1					
Upset stomach	1		1	1		
Vision out of focus					1	
Vomited (number of episodes)	2	1	4		11	
Weak					1	

Treatment A = Taro 1 x 75 mg clomipramine HCl capsules, fed
Treatment B = Basel (Anafranil®) 1 x 75 mg clomipramine HCl capsules, fed
Treatment C = Taro 1 x 75 mg clomipramine HCl capsules, fasted

WF # 74694 sdw. 695 Attachment (5 of 6)

The following is a full statement of the composition of the dosage formulation for Clomipramine Hydrochloride Capsules, 25 mg test batch included in this application:

Item	mg/Capsule	Quantity/Batch
Clomipramine Hydrochloride BP	25 mg	
Pregelatinized Starch NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Capsule Shell		

The following is a full statement of the composition of the dosage formulation for Clomipramine Hydrochloride Capsules, 50 mg test batch included in this application:

Item	mg/Capsule	Quantity/Batch
Clomipramine Hydrochloride BP	50 mg	
Pregelatinized Starch NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Capsule Shell	—	

Wf# 74694 sdw. 659 Attachment (6 of 6)

The following is a full statement of the composition of the dosage formulation for Clomipramine Hydrochloride Capsules, 75 mg test batch included in this application:

Item	mg/Capsule	Quantity/Batch
Clomipramine Hydrochloride BP	75 mg	
Pregelatinized Starch NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Capsule Shell	—	

Unit and Batch Composition

The per batch quantity listed for each ingredient represents the total amount of that ingredient that is actually measured out for the batch. This quantity may, for some ingredients, differ slightly from the theoretical quantity calculated by multiplying the unit composition by the batch size. The reason for this is that all amounts to be measured out are expressed in increments limited to accuracy of the equipment on which they are weighed. In no way is the difference between actual and theoretical per batch quantities related to or provided for in the incorporation of a range for individual ingredients. Exact ingredient amounts are measured out for every batch, as required by the Master Product and Control Record, attached in Section XI at pages 3354.